PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/013619	International filing date *(day/month/year)* 01.12.2004	Priority date *(day/month/year)* 01.12.2003
International Patent Classification (IPC) or national classification and IPC A61K38/18, A61K47/18, A61K47/00		
Applicant BIOGENERIX AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.06.2005	27.01.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Vermeulen, S Telephone No. +49 89 2399-7520

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/013619

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-8	as originally filed

Claims, Numbers

1-12	received on 20.06.2005 with letter of 20.06.2005

Drawings, Sheets

1/4-4/4	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/013619

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	none
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	none
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	none

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The subject-matter of independent claim 1 is considered to meet the requirements of novelty and inventive step (Art. 33(2)-(3) PCT).

None of the documents representing the state of the art discloses a formulation of erythropoietin comprising tris-(hydroxymethyl)-aminomethane (= tris buffer).

The problem to be solved by the present application was providing a erythropoietin formulation which is stable and wherein formation of aggregates even at higher temperatures is reduced or avoided completely.

Stable erythropoietin formulation are provided according to the state of the art by addition of stabilizing amino acids, urea and/or sodium chloride. The majority of the prior art formulations are furthermore buffered with a phosphate buffer. None of the documents however suggests to formulate erythropoietin with tris-(hydroxymethyl)-aminomethane in order to improve stability. Reference is made to table 3 of the description, showing the effect of tris-(hydroxymethyl)-aminomethane on aggregate formation (cf. Formulation B, C and D compared to Formulation A and the prior art Formulation).

Claims 2-12 are dependent on claim 1 and as such also meet the requirements of the PCT with regard to novelty and inventive step.

The formulation defined in claims 1-12 is considered to be industrially applicable and accordingly meets the requirements of Art.33(4) PCT.

PCT/EP2004/013619

20. Juni 2005

BioGenerix AG

Claims

1. A stable pharmaceutical formulation of erythropoietin containing tris-(hydroxymethyl)-aminomethane as stabilizer, whereby the formulation does not contain amino acids or human serumalbumin.

2. A stable pharmaceutical formulation of claim 1 comprising:

a) as a pH buffering agent a sodium phosphate buffer,

b) as stabilizer tris-(hydroxymethyl)-aminomethane in an amount of 10 to 200 mM,

c) a pharmaceutical quantity of erythropoietin.

3. The formulation of claim 2 which comprises NaCl in an amount of 20-150 mM.

4. The formulation according to any of the preceding claims wherein the amount of NaCl ranges from 50 to 100 mM.

5. The formulation of claim 1 to 4 which is an aqueous formulation.

6. The formulation of any of the preceding claims wherein the pH buffering agent has the formula $Na_xH_yPO_4$ wherein x is 1 or 2 and y is 1 or 2 and the sum of x and y is 3 whereby the pH buffering agent is present in the pharmaceutical formulation in a range of 5 mM to 50 mM.

7. The formulation of any of the preceding claims wherein the pH ranges from 5.9 to 6.8, preferably from 6.2 to 6.6.

8. The formulation of any of the preceding claims wherein the tris-(hydroxymethyl)-aminomethane is present in an amount of 20 to 100 mM.

9. The formulation of any of the preceding claims which contains also a non-ionic detergent in an amount ranging from 0.005 to 0.1 % w/v.

10. The formulation of claim 9 wherein the non-ionic detergent is a polysorbate, preferably Tween 20 or Tween 80.

11. The formulation according to claim 10 wherein the polysorbate is not produced from materials derived from animals and wherein the content of peroxide is lower than 1.00 µmol/g.

12. The formulation according to any of the preceding claims which comprises further ethylenediaminetetraacetic acid in an amount of 0.1 to 0.5 mM.